Infectious burden and cognitive function: the Northern Manhattan Study

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Abstract: OBJECTIVE: We hypothesized that infectious burden (IB), a composite serologic measure of exposure to common pathogens (i.e., Chlamydia pneumoniae, Helicobacter pylori, cytomegalovirus, and herpes simplex virus 1 and 2) associated with vascular risk in the prospective Northern Manhattan Study (NOMAS), would also be associated with cognition. METHODS: Cognition was assessed using the Mini-Mental State Examination (MMSE) at enrollment and the modified Telephone Interview for Cognitive Status (TICS-m) at annual follow-up visits. Adjusted linear and logistic regressions were used to measure the association between IB index and MMSE. Generalized estimating equation models were used to evaluate associations with TICS-m and its change over time. RESULTS: Serologies and cognitive assessments were available in 1,625 participants of the NOMAS cohort. In unadjusted analyses, higher IB index was associated with worse cognition (change per standard deviation [SD] of IB for MMSE was -0.77, $p < 0.0001$, and for first measurements of TICS-m was -1.89, $p < 0.0001$). These effects were attenuated after adjusting for risk factors (for MMSE adjusted change per SD of IB = -0.17, $p = 0.06$, for TICS-m adjusted change per SD IB = -0.68, $p < 0.0001$). IB was associated with MMSE 24 (compared to MMSE >24, adjusted odds ratio 1.26 per SD of IB, 95% confidence interval 1.06-1.51). IB was not associated with cognitive decline over time. The results were similar when IB was limited to viral serologies only. CONCLUSION: A measure of IB associated with stroke risk and atherosclerosis was independently associated with cognitive performance in this multiethnic cohort. Past infections may contribute to cognitive impairment.

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Infectious burden and cognitive function

The Northern Manhattan Study

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ABSTRACT

Objective: We hypothesized that infectious burden (IB), a composite serologic measure of exposure to common pathogens (i.e., *Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus, and herpes simplex virus 1 and 2) associated with vascular risk in the prospective Northern Manhattan Study (NOMAS), would also be associated with cognition.

Methods: Cognition was assessed using the Mini-Mental State Examination (MMSE) at enrollment and the modified Telephone Interview for Cognitive Status (TICS-m) at annual follow-up visits. Adjusted linear and logistic regressions were used to measure the association between IB index and MMSE. Generalized estimating equation models were used to evaluate associations with TICS-m and its change over time.

Results: Serologies and cognitive assessments were available in 1,625 participants of the NOMAS cohort. In unadjusted analyses, higher IB index was associated with worse cognition (change per standard deviation [SD] of IB for MMSE was −0.77, $p < 0.0001$, and for first measurements of TICS-m was −1.89, $p < 0.0001$). These effects were attenuated after adjusting for risk factors (for MMSE adjusted change per SD of IB = −0.17, $p = 0.06$, for TICS-m adjusted change per SD IB = −0.68, $p < 0.0001$). IB was associated with MMSE ≤24 (compared to MMSE >24, adjusted odds ratio 1.26 per SD of IB, 95% confidence interval 1.06–1.51). IB was not associated with cognitive decline over time. The results were similar when IB was limited to viral serologies only.

Conclusion: A measure of IB associated with stroke risk and atherosclerosis was independently associated with cognitive performance in this multiethnic cohort. Past infections may contribute to cognitive impairment. ***Neurology*® 2013;80:1209–1215**

GLOSSARY

AD = Alzheimer disease; **CI** = confidence interval; **CMV** = cytomegalovirus; **GEE** = generalized estimating equation; **HSV** = herpes simplex virus; **IB** = infectious burden; **IQR** = interquartile range; **MMSE** = Mini-Mental State Examination; **NOMAS** = Northern Manhattan Study; **OR** = odds ratio; **SES** = socioeconomic status; **TICS-m** = modified Telephone Interview for Cognitive Status; **VIB** = viral burden index.

Basic and clinical research provide evidence that inflammation triggered by infectious agents may play a role in the pathogenesis of ischemic stroke,[1,2] atherosclerosis,[3,4] and dementia.[5] Bacterial and viral infections may invade vessel walls, provoke cytokine release, influence lipid metabolism, and contribute in other ways to vascular dysfunction. Both viral infections, including herpes simplex virus type 1 (HSV-1)[6] and cytomegalovirus (CMV),[7] and bacteria, such as *Chlamydia pneumoniae*[8] and *Helicobacter pylori*,[9] have been associated with cognitive impairment and Alzheimer disease (AD). In prior analyses of the Northern Manhattan Study (NOMAS), a weighted measure of infectious burden (IB) including these pathogens was associated with stroke risk and carotid artery atherosclerosis.[2,4]

Accumulating evidence suggests that cerebrovascular injury and vascular risk factors are associated with cognitive decline and increased risk for AD and other dementias.[10–14] As the population continues to age, health care needs associated with treating and caring for elderly individuals with cognitive decline are projected to pose significant public health and economic burdens.[15]

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Supplemental data at www.neurology.org

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We hypothesized that a measure of chronic infection incorporating several common infections (i.e., *C pneumoniae*, *H pylori*, CMV, and HSV-1 and -2) associated with stroke would also be associated with cognition and cognitive decline in our stroke-free multiethnic cohort.

METHODS

Standard protocol approvals, registrations, and patient consents. The institutional review boards at Columbia University Medical Center and the University of Miami approved the study. All participants gave informed consent to participate in the study.

Description of study population and baseline data collection. The cohort derived from 3,298 multiethnic stroke-free participants enrolled in NOMAS between 1993 and 2001, as previously described.[2] Briefly, participants were ≥40 years of age at enrollment and resided in northern Manhattan, New York, for ≥3 months in a household with a telephone.

Data collection at baseline included vital signs, demographic data, medical history, vascular risk factors, and clinical laboratory parameters including glucose levels and fasting lipid levels. In a subset (n = 984) the number of *APOE* ε4 alleles carried by each subject was determined by *Hha*I digestion of PCR products amplified from genomic DNA. For detailed covariate assessment, see appendix e-1 on the *Neurology*® Web site at www.neurology.org.

Assessment of IB. Blood samples collected at enrollment were centrifuged and frozen at −70°C in 1 mL aliquots until the time of analysis. Since not all participants had blood available for the measurement of all 5 serologies, a subsample of 1,625 was used for the present analysis, as previously described.[2] Serologies were measured using ELISA for the following: *C pneumoniae* (Savyon Diagnostics, Ashdod, Israel), *H pylori*, CMV (Wampole Laboratories, Princeton, NJ), and HSV-1 and 2 (Focus Diagnostics, Cypress, CA). Immunoglobulin G titers were used for all pathogens except *C pneumoniae*, for which immunoglobulin A titers were used based on our previous results.[16,17] All testing was performed in a batch analysis blinded to clinical outcome.

Cognitive assessment. Cognitive status was assessed at baseline using the 30-point Mini-Mental State Examination (MMSE)[18] and at annual telephone interview follow-up using the modified Telephone Interview for Cognitive Status (TICS-m).[19] Testing was performed by bilingual trained research assistants in English or Spanish, depending on language spoken at home.

Statistical analyses. We used IB as the main predictor. Our development of a weighted IB index based on the relationship of individual serologic test results to risk of stroke was described previously.[2] In brief, parameter estimates from Cox proportional hazards model for risk of stroke associated with each serologic result (positive or negative), adjusted for the other serologies, were used to derive a weighted index designated as IB. We constructed models unadjusted and adjusted for demographic and social factors (age, sex, race-ethnicity, education, and insurance status) and vascular risk factors (hypertension, diabetes mellitus, cardiac disease, smoking status, depressive symptoms, reported alcohol consumption, physical activity, cholesterol medication, and lipid levels). Besides age and high-density lipoprotein, all covariates were treated categorically. The rationale for choice of covariates and interactions was based on the literature, biological plausibility, and previous experience with the cohort. We analyzed MMSE as both a continuous and binary outcome (MMSE ≤24 vs >24) based on previously defined thresholds in order to facilitate clinical interpretation.[20] TICS-m was treated as a continuous variable. We fitted linear regression with continuous MMSE to calculate the slope and 95% confidence interval (CI), and logistic regression with MMSE categories to calculate odds ratio (OR) and 95% CI. Generalized estimating equation (GEE) models with exchangeable covariance structure were used to evaluate associations with TICS-m and its change over time. We tested for interactions between IB and all demographic or medical risk factors. Moreover, in a post hoc analysis, we created a viral burden index (VIB) in the same manner as the overall IB index and tested the association of the VIB index with cognition.

We used the inverse probability weighted method to correct for potential selection bias that may have been introduced when the analyzed group was selected from the whole cohort. All hypothesis testing was 2-tailed and p values less than 0.05 were considered significant. All analyses were performed using SAS v9.1.3 (SAS Institute, Cary, NC).

RESULTS

Study population characteristics. The analyzed population consisted of 1,625 subjects (65% women, mean age 69 ± 10 years, 58% Hispanic) with serology measurements (table 1). Characteristics among these participants were similar to those in the overall NOMAS cohort.[2]

Median MMSE was 27 (interquartile range [IQR] 24–29) and median TICS-m over all follow-up measurements was 32 (IQR 27–36). The mean IB index (±SD) was 1.00 ± 0.33 and median 1.08 (IQR 0.91–1.26). The IB index was higher in non-Hispanic black and Hispanic subjects, and in participants with less than high school education, no alcohol intake, and without cardiac disease (table 1).

Association of IB index with MMSE. In unadjusted analysis, higher IB index was associated with lower MMSE as a continuous measure (change in MMSE per SD IB index = −0.77; $p < 0.0001$). After adjusting for demographics and vascular risk factors, the effect was attenuated (change in MMSE per SD IB index = −0.17; $p = 0.06$).

The IB index was associated with greater odds of having MMSE ≤24 compared to MMSE >24 (unadjusted OR per SD IB = 1.58, 95% CI 1.36–1.82). The association persisted after adjusting for demographic and risk factors (adjusted OR per SD IB 1.26, 95% CI 1.06–1.51; table 2).

In subgroup analyses for those with *APOE* genotype available (n = 984), we found that the association between the IB index and MMSE did not change after further adjusting for *APOE* genotype (change in MMSE per SD of IB index = −0.20; $p = 0.06$), and the effect of the IB index on MMSE did not differ by *APOE* genotype (p for interaction = 0.61).

Association of IB index with TICS-m. There was an association of higher IB index and impaired cognition assessed with the TICS-m (difference in baseline TICS-m per SD IB = −1.92; $p < 0.0001$). The effect was attenuated after adjusting for demographics

Table 1 Baseline characteristics[a]

Baseline characteristics of participants	Subjects (n = 1,625)	Median IB index (IQR)	p Value[b]
Sociodemographic risk factors			
Age, y	68.5 ± 10.1	NA	NA
Age <70 y	925 (57)	0.91 (1.09–1.26)	0.526
Age ≥70 y	700 (43)	0.91 (1.09–1.26)	
Female sex	1,054 (65)	0.91 (1.09–1.26)	0.101
Male sex	571 (35)	0.82 (1.09–1.26)	
Non-Hispanic white	295 (18)	0.39 (0.91–1.09)	<0.0001
Non-Hispanic black	333 (21)	0.99 (1.09–1.26)	
Hispanic	945 (58)	0.99 (1.09–1.26)	
Other	50 (3)	NA	NA
Education (≥ high school)	708 (44)	0.69 (1.04–1.17)	<0.0001
Education (< high school)	917 (54)	0.99 (1.09–1.26)	
Medicaid or no insurance	790 (49)	0.99 (1.09–1.26)	<0.0001
Medicare or private insurance	829 (51)	0.82 (1.08–1.26)	
Vascular risk factors			
No physical activity	759 (47)	0.91 (1.09–1.26)	0.079
Any physical activity	866 (53)	0.86 (1.09–1.26)	
No depression	1,443 (89)	0.91 (1.09–1.26)	0.205
Depression[c]	176 (11)	0.89 (1.09–1.26)	
No hypertension	430 (26)	0.82 (1.09–1.26)	0.148
Hypertension[d]	1,195 (74)	0.91 (1.09–1.26)	
No diabetes mellitus	1,279 (79)	0.86 (1.09–1.26)	0.391
Diabetes mellitus	340 (21)	0.91 (1.09–1.26)	
No cardiac disease	1,240 (76)	0.91 (1.09–1.26)	0.043
Cardiac disease	385 (24)	0.86 (1.09–1.26)	
No moderate alcohol intake	1,087 (67)	0.91 (1.09–1.26)	0.044
Moderate alcohol intake[e]	538 (33)	0.82 (1.09–1.26)	
No hypercholesterolemia	590 (36)	0.91 (1.09–1.26)	0.156
Hypercholesterolemia	1,035 (64)	0.86 (1.09–1.26)	
No lipid-lowering medications	1,395 (86)	0.91 (1.09–1.26)	0.060
On lipid-lowering medications	230 (14)	0.82 (1.08–1.26)	
High-density lipoprotein	46.5 ± 14.1	NA	NA
Never smoker	777 (48)	0.91 (1.09–1.26)	0.559
Past smoker	575 (35)	0.86 (1.09–1.26)	
Current smoker	272 (17)	0.86 (1.09–1.26)	
Cognitive assessment			
MMSE score	27 (24–29)	NA	NA
MMSE score <24 points	377 (23)	0.99 (1.17–1.26)	<0.0001
MMSE score ≥24 points	1,246 (77)	0.82 (1.08–1.26)	
Baseline TICS-m	32 (27–36)	NA	NA

Continued

and vascular risk factors, but the association persisted (adjusted change in baseline TICS-m per SD IB index = −0.68; $p < 0.0001$; table 2). We found no association, however, of IB with change in TICS-m over time in analyses either unadjusted or adjusting for demographics and risk factors ($p = 0.13$).

Modification of the association of IB index with cognition. We found interactions of several baseline risk factors (i.e., sex, physical activity, education, and insurance status) with IB index relating to MMSE. The associations between IB index and MMSE were prominent among those who were physically inactive (adjusted change in MMSE per SD IB index = −0.43; $p = 0.001$), women (adjusted change in MMSE per SD IB index = −0.32; $p = 0.007$), those with Medicaid or no insurance (adjusted change in MMSE per SD IB index = −0.44; $p = 0.003$), and those with less than high school education (adjusted change in MMSE per SD IB index = −0.44; $p = 0.002$), while there were no associations among their counterparts. Only physical activity remained an effect modifier when all these interaction terms were included in the final model (p for interaction in the adjusted model = 0.01).

No interaction of demographic or risk factors with IB index, however, was found with regard to a change in TICS-m over time.

Exploratory analyses of viral burden and its association with cognition. Limiting the IB serologies to viral serologies (VIB) resulted in similar findings as for the overall IB index. The VIB index was associated with MMSE ≤24 compared to MMSE >24 (adjusted OR per SD of VIB index = 1.22; $p = 0.04$), as well as with TICS-m (adjusted difference in baseline TICS-m per SD of VIB index = −0.70; $p < 0.0001$), but was not associated with change in TIC-m over time ($p = 0.24$).

DISCUSSION In this multiethnic population-based sample, we found that a measure of IB previously associated with vascular disease risk is independently associated with cognitive performance in cross-sectional analyses. We used well-known and validated measures of cognitive function. Cognitive status was assessed at baseline using the 30-point MMSE[18] and also during annual follow-up using the TICS-m.[19] These results are consistent with prior studies identifying an association between chronic infections and both cognition[5–8,21–27] and vascular risk,[2–4,28,29] but we further extend prior findings by using a novel weighted average of IB associated with vascular disease risk and by using complementary measures of cognitive function. Our study results point to the possibility that the same cumulative index of pathogens may be a common risk factor for both stroke and cognitive impairment.

Interestingly, we found a more pronounced association of IB with MMSE when treated as a

Table 1 Continued

Baseline characteristics of participants	Subjects (n = 1,625)	Median IB index (IQR)	p Value[b]
Infectious burden		NA	NA
IB index	1.00 ± 0.33	NA	NA

Abbreviations: IB = infectious burden; IQR = interquartile range; MMSE = Mini-Mental State Examination; NA = not applicable; TICS-m = modified Telephone Interview for Cognitive Status.
[a] Values are mean ± SD, n (%), or median (IQR).
[b] Wilcoxon/Kruskal-Wallis test.
[c] Depression is defined as a Hamilton Depression Rating Scale score >10 or a history of antidepressant use.
[d] Hypertension defined by history, taking medications, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg.
[e] Moderate alcohol intake: one alcoholic drink per week up to 2 drinks per day; sporadic missing baseline data but not less than n = 1,619.

dichotomous variable compared to MMSE as a continuous variable. This might point to a threshold effect or that only a major change in MMSE is associated with a higher IB. The use of the 24-point threshold to define cognitive impairment in Hispanic patients has been a matter of debate since it is not very well documented in this ethnic group,[20] but this threshold has been used widely in the literature to describe cognitive impairment and therefore permits comparison with previous studies.

Additionally, we found that the effect of IB on cognitive impairment may depend on certain demographic and vascular risk factors. In general, we found that the magnitude of effects of IB was greater among women, those with lower socioeconomic status (lower levels of education and health insurance), and the physically inactive. The association was most prominently modified by participants' physical activity levels. Among physically inactive participants, a higher IB index was associated with a lower MMSE, while there was no association among physically active participants. This result should be considered exploratory, however, as we investigated multiple interactions. Nevertheless, this observation provides some indirect evidence that the negative effects of chronic infection might be mitigated by beneficial behaviors such as physical activity, and evidence is accumulating that exercise has anti-inflammatory effects.[30]

IB was not associated, however, with cognitive decline over time, and we did not find any interactions for this with baseline risk factors. The absence of an association with cognitive decline over time could reflect the relatively advanced state of cognitive impairment at the time participants in our relatively elderly cohort were enrolled, limiting our ability to detect further decline with time. Our duration of follow-up, moreover, may have been insufficient to detect a change. Finally, it is possible that a practice effect, such that participants improve scores on cognitive tests over time, may have limited our ability to detect an effect.

Human and animal studies provide evidence that chronic infections with HSV-1, HSV-2, CMV, HIV-1, *C pneumoniae*, and *H pylori* are associated with an elevated risk of cognitive impairment and different forms of dementia.[5–8,21–27] Most of these previous studies were focused on one specific pathogen and the few studies that examined multiple pathogens simultaneously assumed equal weight for each investigated pathogen. For example, one study investigated 400 randomly selected home-dwelling individuals with cardiovascular diseases.[5] The primary endpoint was cognitive impairment, defined as MMSE score <24 points at baseline and after 1 year of follow-up. Viral burden at baseline was defined as the number of seropositivities toward HSV-1, HSV-2, and CMV equally divided into 3 categories (0 to 1, 2, or 3). The lowest category was a combination because few people had zero viral seropositivities. Bacterial burden was defined as seropositivities toward *C pneumoniae* and *Mycoplasma pneumoniae* divided into 3 categories (0, 1, or 2). Logistic regression was performed with the categories of viral or bacterial burden, various risk factors, and demographic data as independent variables. In subjects with 3 viral seropositivities (compared to 1), the

Table 2 Association of the infectious burden index with cognitive function[a]

	Unadjusted	Adjusted for demographics[b]	Adjusted for demographics, general, and vascular risk factors[c]
MMSE			
Difference in baseline MMSE per SD in IB	−0.77 (−0.95 to −0.58); <0.0001	−0.16 (−0.34 to −0.002); 0.08	−0.17 (−.34 to 0.01); 0.06
MMSE ≤24	1.58 (1.36 to 1.82); <0.0001	1.23 (1.04 to 1.45); 0.019	1.26 (1.06 to 1.51); <0.01
TICS-m			
Difference in baseline TICS-m per SD in IB	−1.92 (−2.24 to −1.61); <0.0001	−0.66 (−0.93 to −0.37); <0.0001	−0.68 (−0.97 to −0.39); <0.0001
Annual change in TICS-m per SD in IB	0.03 (−0.01 to 0.07); 0.18	0.03 (−0.01 to 0.07); 0.13	0.03 (−0.01 to 0.07); 0.13

Abbreviations: IB = infectious burden; MMSE = Mini-Mental State Examination; TICS-m = Telephone Interview for Cognitive Status.
[a] Values are β coefficient or odds ratios with corresponding 95% confidence interval and p values.
[b] Adjusted for age, sex, race-ethnicity, education, and insurance status.
[c] Adjusted for age, sex, race-ethnicity, education, insurance status, depressive symptoms, physical activity, reported alcohol consumption, hypertension, any cardiac disease, diabetes mellitus, dyslipidemia, high-density lipoprotein, lipid-lowering medication, and smoking status.

adjusted hazard ratio for cognitive impairment at baseline was 2.5 (1.3–4.7) and after 1 year it was 2.3 (1.2–4.6). However, no association was observed between cognition and bacterial burden. Another investigator studied a subset (n = 1,204) of the participants in the Sacramento Area Latino Study on Aging.[24] Baseline serum samples were assayed for levels of immunoglobulin G antibodies to CMV and HSV-1. Participants were screened annually over a 4-year period for cognitive function (by MMSE) and episodic memory (by Delayed Recall Scale scores). They found a higher rate of cognitive decline over the 4-year period in subjects with the highest CMV antibody levels at baseline than in individuals with the lowest levels ($p = 0.003$). Unlike these studies, we did not assume that each infection should be associated with a similar risk of cerebrovascular disease or cognition, and we implemented a novel weighted average of IB that was previously associated with cerebrovascular events. However, since previous studies showed associations primarily with viruses, we also performed an exploratory analysis to assess whether the driving force behind the association of IB index with cognition might be the viral pathogen burden. The estimates for the associations with cognition using viral serologies alone were almost identical to those using a combined bacterial and viral score, providing support for the notion that most of the effect of IB on stroke and cognition is mediated through viral rather than bacterial serologies.

The mechanism for this association remains uncertain. It may be that chronic infection due to these pathogens contributes to the overall inflammatory milieu and, together with other risk factors, leads to atherosclerosis, subclinical stroke, and dementia. Inflammation in brain vessels has been postulated to play an important role in both vascular dementia and AD.[31] In addition, a direct toxic effect of some neurotropic agents may play a role in the development of cognitive impairment.[32,33] Further studies are required to establish the pathogenic mechanisms.

In our univariate analysis, we found an association of IB index with insurance status and education, both proxies for socioeconomic status (SES), as well as race-ethnicity. In the multivariate analysis after adjusting for these demographic variables, the association of IB index with cognition was attenuated. It might be that the known socioeconomic gradients concerning the incidence of cognitive impairment[34] are partly explained by a higher IB.[35] For example, data from the National Health and Nutrition Examination Survey III addressed socioeconomic and race-ethnic differences in infection status in the United States.[36] *H pylori*, CMV, HSV-1, and hepatitis B virus were used for the infection burden analyses.[36] The authors found that individuals with less than high school education had roughly 50% increased risk of having an additional infection compared with high school graduates, whereas those with postsecondary education had 50% lower odds.[36] Income had similar effects, whereby low income was associated with 33% higher odds of an additional infection, and high income with 45% lower odds, compared with the middle-income group.[36] This association might be due to a higher exposure rate but it might also be due to an initial susceptibility to infections triggered by socioeconomic stressors. There is evidence of an association between low SES, increased stress, and enhanced susceptibility to several viruses.[37]

Our study has limitations. Because it is cross-sectional, we cannot make conclusions about the direction of associations. The infections we investigated, however, most likely preceded the development of cognitive impairment, since the antibody pattern reflects chronic infectious status and representative studies have shown that the majority of CMV and HSV-1 infections occur in childhood.[38,39] Second, it was not possible to examine the relationship between infection and specific forms of cognitive impairment. For example, earlier research has shown that CMV DNA is found in a higher proportion of brains of people with vascular dementia than in age-matched controls.[7] Third, we did not use detailed neuropsychological testing in our analyses. However, both the MMSE as well as the TICS-m are well-established tools to assess cognitive performance in large cohorts. Fourth, we did not have *APOE* genotype information in all subjects. However, in the subgroup analyses, we found that IB index was independently associated with cognition even after adjusting for *APOE* genotype, and the effects of IB index on cognition did not differ by *APOE* genotype. These findings should be interpreted with caution due to potential selection bias. Finally, a few factors may have reduced the ability to detect a strong association between IB index and cognitive decline over time in our study. For example, a moderate practice effect over the follow-up period might have played a role, or a threshold effect, indicating that when the damage is already done there is no further decline.

The strengths of this study include the population-based multiethnic cohort, including a large proportion of Hispanic subjects, who are frequently underrepresented in studies of cognition, and the ability to adjust for numerous potential covariates. In addition, GEE analyses were used to model corresponding trajectories of cognitive decline.

Our results need to be validated in independent populations before they can be generalized. If confirmed, however, these findings could have potential clinical implications. For example, treatment and eradication of these pathogens might have a positive impact on cognition as well as stroke, thereby addressing 2 major causes of neurologic disease

burden worldwide. In the case of viral pathogens, early childhood vaccination or antiviral treatment could decrease stroke risk and cognitive impairment. Based on our data, early intervention might be more promising, since there was no association with decline over time in this elderly cohort.

Our results extend the findings of previous studies aimed at investigating the association of chronic infections and cognitive performance and specifically point to IB as a common risk factor of both stroke and cognitive impairment.

AUTHOR CONTRIBUTIONS

Study idea and planning of analysis: Mira Katan and Mitchell S.V. Elkind. Statistical analysis: Yeseon P. Moon, Myunghee C. Paik. Interpretation of the data: Mira Katan, Yeseon P. Moon, Myunghee C. Paik, Ralph L. Sacco, Clinton Wright, and Mitchell S.V. Elkind. Drafting of the manuscript: Mira Katan. Critical revision of the manuscript: Mira Katan, Yeseon P. Moon, Myunghee C. Paik, Ralph L. Sacco, Clinton B. Wright, and Mitchell S.V. Elkind. Obtaining funding: Mira Katan, Ralph L. Sacco, and Mitchell S.V. Elkind.

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DISCLOSURE

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